REMARKS

Applicants wish to thank the Examiner for her assistance in defining the restricted subject matter. Applicants respectfully request entry of amendments to claims 24 and 25, and new claims 33-51. Please withdraw claims 1-23 and 26-32, without prejudice or disclaimer.

Support for the amendments can be found throughout the specification, including paragraphs [0046], [0050], [0058], [0153], [0159], and the originally filed claims and, therefore, do not add new matter.

Applicants submit that pending claims 24, 25, and 33-51 are in condition for allowance, and respectfully request that the claims as amended be entered.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 24 and 25 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

Applicants traverse the rejection as it might apply to the new and amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the use of "terminal nucleotide" is confusing because primers ending at position 300 do not seem to correlate with the election of a primer having the sequence of nucleotides 275-350 of SEQ ID NO:20614. Applicants respectfully disagree.

Review of the sequence represented by SEQ ID NO:20614 shows that position 300 is denoted by the symbol "r." Thus, primers comprising, for example, residues 275-300, which have "a" or "g" as the terminal nucleotide meet the claim element. Further, the claims include complements. Complementary primers would necessarily be upstream from sense strand position 300. Based on the claim elements, such complementary primers would comprise sequences up to residue 350 upstream from residue 300 of SEQ ID NO:20614, and one of skill in the art would know the position of the terminal nucleotide of such complementary primers since the claim specifically recites that the primers are "complementary to a specific sequence variant which comprises the SNP position." Therefore, as the terminal nucleotides would be defined by

being complementary to the SNP position, where the residues as elected would comprise sequences which are adjacent to such SNP position, one of skill in the art of designing primers would understand the metes and bounds of the claims.

The term "extension primer" is a term of art and would be known to one of skill in the art generally as an oligonucleotide sequence which extends nucleotide sequences from its 3' end by the use of an enzyme (e.g., a polymerase or ligase). As the claims recite that the extension primer (which is distinguished from the first and second primers) binds downstream from other primers, and given the functional properties associated with the term, one of skill in the art would understand the extension primer was not a probe. As such, one of skill in the art would understand the metes and bounds of the term.

For these reasons, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 24, and 25 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description support.

Applicants traverse the rejection as it might apply to the new and amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that as the specification does not disclose any sequences that are 90% identical to the SEQ ID NO recited or any homologous sequences, that the claims do not meet the written description requirement. Applicants respectfully disagree.

The claims no longer recite a polynucleotide that is at least 20 nucleotides in length and is at least 90% identical to a fragment of at least 20 contiguous nucleotides of a bovine genome, so this aspect of the rejection is moot. However, the claims as amended recite that each primer "comprises at least 20 contiguous nucleotides which are at least 90% identical to the sequences upstream and adjacent to the SNP position." The variation in sequence for the primer elements as claimed are within 20 nucleotides of the SNP site (i.e., position 300) and as such, would only include a variation of a limited number of bases (e.g., 2), and not 600 as recited in the Action. Further, such variations may be used in the application of methods of identification as recited in the specification as filed (e.g., allele specific PCR).

For example, at paragraph [0080] the specification expressly recites:

> "Numerous methods for identifying haplotype alleles in nucleic acid samples are known in the art. In general, nucleic acid occurrences for the individual SNPs are determined and then combined to identify haplotype alleles. There are several algorithms for haplotype reconstruction based on pedigree analysis. These are the Maximum Likelihood method ((Excofier, L., and Slatkin, M., Mol. Biol. Evol. 12: 921-927 (1995)), the parsimony method created by Clark, A. G., Mol. Biol. Evol. 7: 111-122 (1990) and the phase reconstruction method of Stephens, M., et al., Am. J. Hum. Genet. 68:978-989, 2001, which is incorporated herein by reference) can be applied to the data generated regarding individual nucleotide occurrences in SNP markers of the subject, in order to determine alleles for each haplotype in a subject's genotype. Alternatively, haplotypes can also be determined directly, for each pair of sites, by allele-specific PCR (Clark, A. G. et al., Am. J. Hum. Genet. 63: 595-612 (1998)." (Emphasis added).

Primers for allele specific PCR may comprise primers which have mismatches at the 3' end or mismatches located within the primer (see, e.g., Nollau and Wagener, Methods for Detection of Point Mutations: Performance and Quality Assessment, Clin Chem (1997) 43:7:1114-1128, at page 1123, col. 2, first paragraph; Exhibit A). Further, allele specific PCR may comprise internal controls to exclude false negative results (e.g., for heterozygosity, where variants comprising point mutations in addition to the target point mutation must be accounted for; Id., at paragraph 2). Moreover, such primers for use in allele specific PCR may comprise additional stretches of non-complementary nucleotides at the 5' end (Id., at paragraph 3). Therefore, because support for written description standard does not require a re-description of what was already known (see, e.g., Capon v. Eshhar, 76 U.S.P.Q.2d 1078 (Fed. Cir. 2005)), and as the variation of bases in the primers to account for such targets that are heterozygous would reasonably convey to one of skill in the art that Applicants possessed primers with the characteristics necessary to perform a method of identification embraced by the claim (see, e.g., Fujikawa v. Wattanasin, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), Applicants submit that the written description standard has been met.

For these reasons, Applicants respectfully request that the rejection be withdrawn.

Claims 25 and 26 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

Applicants traverse the rejection as it might apply to the new and amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the specification is not enabling for the scope of the claims.

Applicants submit that it seems counter-intuitive to compact prosecution that on the one hand Applicants are forced, by Restriction, to select specific sequences for examination based on arguments that SNPs as claimed share no similarity in design, operation or effect, and then arguments are presented against Applicants stating that that the sequences offered by the Action in the Restriction, and accepted by Applicants, must be used with other sequences; i.e., sequences that share similarity in design, operation or effect.

Nevertheless, while not acquiescing to the reasoning offered in the Action, in order to expedite prosecution toward allowance, the claims have been amended to recite that each primer "comprises at least 20 contiguous nucleotides which are at least 90% identical to the sequences upstream and adjacent to the SNP position."

Applicants submit, that while it is appropriate to recognize variability in determining the scope of invention, determination of what is needed to support generic claims to biological subject matter depends on a variety of factors including 1) knowledge in the particular field, 2) the extent and content of the prior art, 3) the maturity of the science or technology, and 4) the predictability of the aspect at issue. Capon v. Eshhar, 76 U.S.P.Q.2d 1078, 1084, 418 F.3d 1349, at 1356 (Fed. Cir. 2005).

The Action presents statements from articles to support the position that the art is unpredictable regarding gene associations, citing Lucentini et al., Wacholder et al., and Ioannidis. However, review of these articles demonstrates that they are focused on disease states in humans, not cattle, where human populations cannot be controlled for factors that are expressly required for animal husbandry; i.e., control reproduction to create specific

domesticated breeds of animals. For example, the ability to clone domesticated animals such as sheep and cows exists. For humans, it is not only ethically problematic, but also scientifically unproved, and it is not clear that the technology exists to carry out such processes, in humans, that are readily available/used in animals. Therefore, the attempt to compare findings/manipulations related to genetics and human disease with that which is possible for the analysis of animals is inappropriate.

Regarding Heaton et al., the examples recited by the Action focus on animal identity and kinship, not on SNPs and particular traits. Further, even where Heaton et al. is alleged to provide support for the "significant problem . . . for spurious associations (i.e., false positives) that arise from unrecognized population stratification or recent admixture," they provide the solution in the very next sentence (i.e., use of unlinked SNPs). Applicants respectfully submit, that while such references may provide support for disparaging the efficacy of genetic analysis, efficacy is not relevant to enablement analysis (see, e.g., Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318 (Fed. Cir. 2005), and would submit further that these references do not support the position in the Action that art recognized problems exist.

Further, it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize the generic invention. See, e.g., In re Angstadt, 537 F.2d 498, 504 (CCPA 1976). Accordingly, generic inventions are not *per se* invalid because success for each possible iteration is not assured. Capon, at 1357.

Respectfully, enablement requires that a specification teach those of skill in the art how to make and use the claimed invention without undue experimentation (see, e.g., In re Wright, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993)). In other words, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention (see, e.g., Northpoint Technology, Ltd. V. MDS America, Inc., 413 F.3d 1301 (Fed. Cir. 2005)). Moreover, the enablement standard is met if the description enables any mode of making and using the claimed invention (see, e.g., Engel Industries, Inc. v. Lockformer Co., 20 U.S.P.Q.2d 1300 (Fed. Cir. 1991)). Also, it must be kept in mind that Applicants need not provide any

examples (see, e.g., M.P.E.P. §2164.02), nor are Applicants limited to only those examples provided to enable a feature under §112 (see, e.g., Callicrate v. Wadsworth Manufacturing Co., 427 F.3d 1361 (Fed. Cir. 2005)).

Applicants submit that the specification expressly teaches a) how to generate a high density bovine genetic SNP map. For example, paragraph [0198] expressly states:

> "Shotgun sequencing was performed with four different bovine subjects that represented several different breed types: Angus, Limousin, Brahman and Simmental. Upon whole genome assembly of the sequenced fragments, contigs were formed from consensus sequence, and sequence variants were identified and cataloged. 786,777 sequence variants that differed by a single nucleotide became candidate SNP markers for the high-density SNP map. The relative position of each candidate SNP within the bovine genome was determined using the assembled human genome as scaffolding creating a candidate map of 242,181 human-mapped markers. Upon positioning of the SNPs within the genome, individual markers were tested to determine informativeness within the cattle population using 210 animals representing diverse breeds (Angus, Charolais, Limousin, Hereford, Brahman, Simmental and Gelbvieh) and Mendialian segregation (21 trios of parents and progeny). Selected markers were polymorphic in the majority of the breeds tested. Any markers within a region that failed the test were discarded and replaced with another marker in the region. These markers were also validated against the test population. This process was repeated until a relatively evenly distributed genetic SNP map was obtained, where the average genetic distance between any two adjacent markers is 0.5 cM."

Thus, SNPs were selectively chosen to fall within the average genetic distance as claimed.

The specification also teaches b) identification of bovine SNPs associated with tenderness. For example, the specification expressly recites at paragraphs [0200]-[0202]:

> "DNA samples from bovine subjects were obtained by collecting 50 ml of whole blood from the 4,791 bovine subjects. 25 ml of whole blood was used for DNA

extraction using standard methods and concentrations of DNA were calculated using standard fluorimetric methods. Animals representing less than or equal to the 10th percentile of low numeric phenotypic animals (44 individuals) and the 90th percentile and greater of high phenotypic animals (44 individuals) were identified for each trait. The low numeric values were identified as "Low" and the high numeric values were identified as "High". DNA samples were pooled from bovine individuals that represent high and low phenotypic extremes for the expression of a target trait in a population of bovine animals with each of the 44 animals contributing equally to the pool of DNA. A separate "High" and "Low" pool was created for each biological type (English, Continental, and Brahman crosses) by treatment group (Early, Optimum, Late) for each of the five traits resulting in 90 total pools. In addition to the 90 pools listed above, another group was formed based on animals that were 5 standard deviations above the mean for numeric tenderness values. Eleven animals were included in this group of individuals and the pool was compared to the other tenderness groups resulting in a total of 91 pools. Each pool was tested against each of the 6189 mapped and validated SNP markers. The SNP detection platform utilized in the experiment was the Beckman Coulter SNP-IT system, utilizing single-base extension of the SNP base. Allele frequency was estimated for each pool based on the fluorescence intensity of each of the two incorporated fluorescent labels corresponding to the SNP alleles. These estimates were adjusted for marker specific characteristics and incorporation differences. A test statistic was developed based on a Chi-square distribution of differences among allele frequencies of the high minus low pools. These test statistics were summed across the 9 breed by treatment groups within each trait resulting in Chi-square distribution. SNP markers reaching a threshold test statistic of 46.96294 for the trait of tenderness and 21.66599 ($p<0.01$) for the remaining four traits of retail yield, daily gain, fat thickness and marbling were identified as associated SNPs and are listed in Tables 1A and 1B.

The high-density SNP map was used to identify SNPs that are associated with a series of bovine traits. The traits included marbling, tenderness, fat thickness, yield, and daily gain. Tables 1A and 1B (filed herewith on a compact disc) provide the identity of SNPs that associated with one or more of the traits analyzed. Twenty five hundred and ten associated SNPs were identified for all five traits.

Table 1A provides the following information, from left to right columns: SNP name; a sequence identifier of the sequence listing filed herewith, for an amplicon, wherein the SNP position is position 300 of the amplicon; position of the SNP within the amplicon (i.e. position 300); The nucleotide sequence and SEQ ID NO: for an extension primer capable of priming polynucleotide synthesis across the SNP position; trait(s) that are associated with the SNP; Characteristics of the trait that are associated with specific nucleotide occurrences at the SNP; Nucleotide occurrences that have been detected at the SNP position; And the sequence identifier of contig sequences that are located within 500,000 nucleotides from the SNP on the bovine genome. Table 1B provides the following information from left to right columns: SNP name; A sequence name of a contig that includes the SNP position, as well as the position numbers within the contig for an amplicon that includes the SNP; Position of the SNP within the amplicon (i.e. position 300); The nucleotide sequence for an extension primer capable of priming polynucleotide synthesis across the SNP position; trait(s) that are associated with the SNP; Characteristics of the trait that are associated with specific nucleotide occurrences at the SNP; Nucleotide occurrences that have been detected at the SNP position; And the sequence identifier of contig sequences that are located within 500,000 nucleotides from the SNP on the bovine genome."

From these passages, the specification specifically recites how the particular SNPs for the traits were correlated, including the use of primers directed to position 300, the use of extension primers for priming synthesis across the SNP position and characteristics of the nucleotide occurrences that have been detected at the SNP position, and where the SNPs are located which are within the average genetic distance as claimed.

Example 3 discusses how individual SNPs were used that are within the average genetic distance as claimed (e.g., at paragraph [0209]; SNP9 (MMBT03905), significantly associated with vision retail yield). As such, the specification provide guidance on how to make and use an individual SNP associated with a trait using the elements as outlined in the claims.

To reiterate, Applicants submit that the specification provides specific guidance for how to generate a high density bovine genetic SNP map, how to identify bovine SNPs associated with tenderness, and how to use a single SNP that is associated with a specific trait; i.e., how to practice the invention commensurate in scope with the claims. And while the procedures as disclosed involve some level of technical manipulation, because such methods and steps are routinely used in the art, such procedures do not rise to the level of undue experimentation. (See, e.g., Johns Hopkins University v. Cellpro, Inc., 47 U.S.P.Q.2d 1705, 152 F.3d 1342 (Fed. Cir. 1998), where the court stated that "experimentation does not constitute undue experimentation" where "it is merely routine.").

Therefore, the claims are enabled because the specification provides appropriate guidance and working examples such that one of skill in the art could practice the invention as claimed, in the absence of undue experimentation.

For these reasons, Applicants respectfully request that the rejection, including as it may be applied to the amended claims, be withdrawn.

Conclusion

Applicants submit that pending claims 24, 25, and 33-51 are in condition for allowance. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

Please charge the Petition for Three Month Extension fee of $1020.00 to Deposit Account No. 07-1896. The Commissioner is hereby authorized to charge any additional fees required by this submission, or make any credits or overpayments, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: August 27, 2007

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